REMARKS

An IDS is submitted herewith. Applicant asks that the references be considered.

Claims 1-19 and 32-42 are pending in the case. In response to a restriction requirement, applicant cancelled claims 20-31 as being directed to non-elected inventions, and added claims 37-42. Of the added claims, the Office Action has entered claims 37-40 into the case, and has withdrawn claims 41 and 42 as being directed to a non-elected inventions.

Independent claims 1 and 32 are currently amended, as are dependent claims 7 and 34. Claims 43-46 are newly presented. Support for the amendments to the claims is found, e.g., at paragraph [0009] and paragraph [0011] of the published application (US 2004/0259832). Support for the newly presented claims is found, e.g., in original claims 3-6 and 8. No new matter has been added.

Elections/Restrictions

The Office Action states at page 2 that "newly submitted claims 41-42 are directed to an invention that is independent or distinct from the invention originally claimed." At page 3, the Office Action states "since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected." The Office Action goes on to state at page 3 that "claims 41-42 are withdrawn from consideration," but that "claims 37-40 directed to kits comprising antiherpes substances are grouped with the elected group I and are examined on their merits herein."

Applicant accepts this restriction without traverse. Therefore, claims 1-19, 32-40, and 43-46 are now under consideration.

Claimed Inventions

Claims 1 and 32 are independent in form. Amended claim 1 features compositions that include a combination of an inhibitor of Herpes simplex virus thymidine kinase that is selected from the group consisting of 2-phenylamino-9-substituted-6-oxopurines and 2-phenylamino-9H-6-oxopurines, or an ester, salt, or solvate thereof, and an antiherpes substance that inhibits viral DNA replication that includes one or more of (1) a pre-phosphorylated or phosphonate

nucleoside analog; (2) a pyrophosphate analog; and (3) a nucleoside analog, or any combination thereof, or an ester, salt, or solvate thereof. Amended claim 32 features kits for treatment of a Herpes simplex virus infection in a mammal that include (a) an inhibitor of Herpes simplex virus thymidine kinase that is selected from the group consisting of 2-phenylamino-9-substituted-6-oxopurines and 2-phenylamino-9H-6-oxopurines, or an ester, salt, or solvate thereof, (b) an antiherpes substance that inhibits viral DNA replication that includes one or more of (1) a pre-phosphorylated or phosphonate nucleoside analog; (2) a pyrophosphate analog; and (3) a nucleoside analog, or any combination thereof, or an ester, salt or solvate thereof, and instructions for administering (a) and (b) concurrently or within a sufficiently close time to achieve coexistent concentrations of (a) and (b) in subject. New independent claims 43 and 45, which are directed to a composition and a kit, respectively, require specific inhibitors and antiherpes substances; namely 2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine, or an ester, salt, or solvate thereof as inhibitor, and one or more of foscarnet, acyclovir, and cidofovir or an ester, salt, or solvate of any of these antiherpes substances.

As described in the present specification, the inhibitor of Herpes simplex virus (HSV) thymidine kinase (TK), and the antiherpes substance that inhibits viral DNA replication provide an unexpected synergistic effect in activity against recurrent Herpes simplex infections, and Herpes simplex encephalitis. Except for active antiviral therapy, which inhibits viral DNA replication (e.g., by inhibiting viral DNA polymerase), and prophylactic acyclovir in certain cases, there are few (if any) therapies available to prevent recurrences, or to prevent asymptomatic viral shedding and infectivity. This invention, therefore, represents a major breakthrough in the treatment of recurrent Herpes simplex infections, and Herpes simplex encephalitis.

35 U.S.C. § 112, Second Paragraph

Claims 1-19 and 32-40 have been rejected as being allegedly indefinite. In particular, the Office Action states at page 5 that the term "analog" in these claims render the claims indefinite. The Office Action continues on the same page that "one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired."

Applicant respectfully submits that the metes and bounds of the term "analogs" with respect to the claimed classes of molecules is well understood by those of ordinary skill working in the field of herpes infections. As evidence that this is indeed the case, applicant submits herewith excerpts from an NIAID Chemical Database (of the National Institutes of Health) that describes "nucleoside analogs," such as AZT, 3TC, ddI, ddC, D4T and abacavir succinate; a GlaxoSmithKline datasheet for ZOVIRAX® (acyclovir), describing acyclovir as "a synthetic nucleoside analogue," and a paper describing the rational design of antiviral drugs, such as "nucleoside analogs" and "pyrophosphate analogs." Since a person of ordinary skill in the art would understand the term "analogs," the term is definite. As such, applicant respectfully requests that the rejection be withdrawn.

35 U.S.C. § 112, First Paragraph

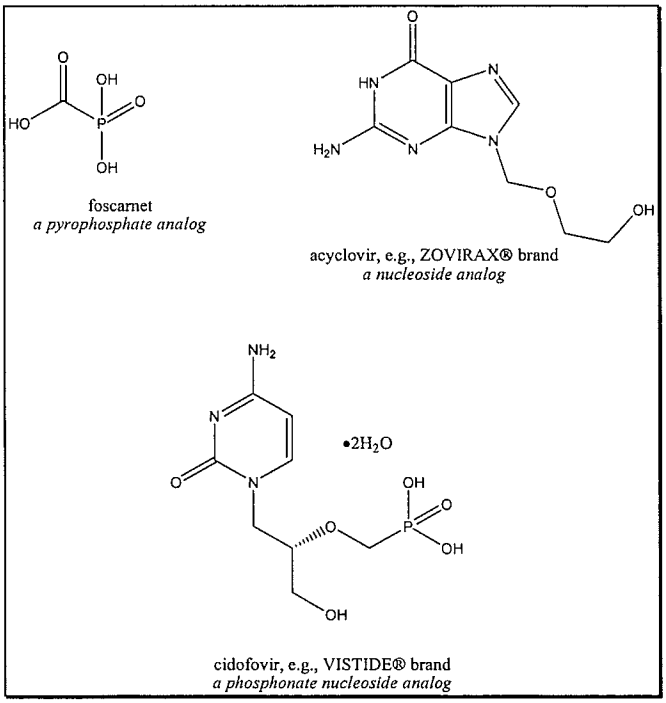
Claims 1-19 and 32-40 have been rejected as allegedly lacking enablement. In particular, the Office Action states at page 6 that "the specification, while being enabling for one of a composition comprising 2-phenylamino-6-oxo-9-(4-hydroxybutyl)purine (HBPG) and foscarnet or acyclovir or cidofovir, does not reasonably provide enablement for the combination of any inhibitor of Herpes simplex virus thymidine kinase with **any** antiherpes substance comprising one or more of a pre-phosphorylated or phosphonate nucleoside analog, a pyrophosphate analog or a nucleoside analog."

Applicant acknowledges that the Office Action has recognized that certain aspects of the claimed invention are enabled, but respectfully submits that in fact the full scope of the claims is enabled. First, applicant is claiming compositions and kits and not methods of use as the Office Action alleges. Thus, the specification must teach how to make and how to administer the claimed compositions and how to use the kits. Applicant submits that the specification fully meets this requirement.

The claimed compositions require two components, an inhibitor of HSV TK and an antiherpes substance that inhibits viral DNA replication, and the specification fully describes how to obtain or make each of these components and how to combine them. For example, in paragraph [0030] of the published application, applicant references Wright, U.S. Patent No. 5,646,155 ("Wright '155"), and the compound identified in the Office Action (HBPG). Wright

'155 discloses many HSV TK inhibitors, along with their synthesis and characterization. For example, Table 1 of Wright '155 shows the concentration of nine compounds, the last being HBPG, at which fifty percent of either HSV1 or HSV2 TK inhibition is observed. Thus, having access to the present specification, along with Wright '155, a person of ordinary skill in the art would have in their possession the suitable TK inhibitors, and would have test methods for determining HSV TK inhibition for other suitable TK inhibitors that may not be described in Wright '155. Applicant respectfully submits that an inhibitor of Herpes simplex virus thymidine kinase, as each independent claim requires, is fully enabled.

With respect to an antiherpes substance that inhibits viral DNA replication, this class of compounds is readily known to a person of ordinary skill in the art (see, e.g., the NIAID Chemical Database referenced above). The present specification also discloses numerous examples. Applicant provides working examples with foscarnet, acyclovir, and cidoforvir, and notes this is a structurally diverse set of molecules (structures shown below). The test results in the application support applicant's assertion that since three such diverse molecules worked, that other molecules within these diverse classes of molecules would also work in a similar fashion. Thus, applicant respectfully submits that the antiherpes substance that inhibits viral DNA replication is fully enabled as well.



With respect to the claimed combination of the HSV TK inhibitor, and an antiherpes substance, the specification also describes how to combine these two components and how to administer them concurrently (see, e.g., paragraph [0041]).

Thus, applicant respectfully submits that a person of ordinary skill armed with the teachings of Wright '155 and the present specification could fully make and use the claimed invention without undue experimentation because the level of skill in the art is high ("PhD, M.D. or equivalent advanced degree" as admitted by the Office Action at page 7), and because considerable guidance and direction is given in the specification, as discussed above. Thus, applicant respectfully submits that the claims are fully enabled, and requests that the rejection be withdrawn.

35 U.S.C. § 103

Claims 1-19 and 32-40 have been rejected as being allegedly obvious over Wright '155 in view of Naesens et al., Herpes, 8(1), 2001 ("Naesens"). The Office Action at page 11 cites a passage in Wright '155 found at col. 9, lines 59-62, which is reproduced below.

> The compounds of the invention can be used as the sole active agents, or can be used in combination with other active ingredients, e.g., direct antiviral drugs, growth factors which could facilitate neuronal survival in neurological diseases, or peptidase or protease inhibitors.

The Office believes that it would have been obvious at the time of invention "to make a composition comprising a combination of an inhibitor of Herpes Simplex virus thymidine kinase and an antiherpes substance comprising one or more of a pre-phosphorylated or phosphonate nucleoside analog, a pyrophosphate analog and a nucleoside analog since Wright et al. [Wright '155] discloses pharmaceutical compositions comprising a herpes simplex virus thymidine kinase inhibitor and suggest the combination with other direct antiviral drugs (page 12 of the Office Action, first paragraph). Apparently, the Office Action believes that Naesens, which "discloses a series of antiherpes substances including acyclovir, ganciclovir, foscarnet and brividin" (page 11 of the Office Action, last paragraph) provides what is missing in Wright '155. Applicant respectfully disagrees, and requests reconsideration in light of the following remarks.

The limitations of each pending independent claim have been discussed above. Applicant respectfully submits that the passage cited in Wright '155 (above) is vague, and would not have led a person of ordinary skill in the art to the presently claimed inventions. For the sake of argument, even if the Office has established a *prima facie* case of obviousness, a conclusion that is not shared by applicant, the present application provides clear evidence of unexpected results that rebuts any such a conclusion. For example, at paragraph [0049], application describes experiments with respect to a combination of HBPG and foscarnet (emphasis added).

> The results of Table 1 establish dose-response relationships for the effect of each compound when administered individually to mice to be used against encephalitis caused by HSV1 and HSV2. The results of Table 2 illustrate the effect of combining suboptimal doses of HBPG and foscarnet in treatment of HSV2 encephalitis, **showing clear synergistic effect of the combinations**. For example, the combination of 50 mg/kg of each compound protected 50% of mice from HSV2 encephalitis, whereas simple addition of the compound effects would be expected to protect only 10% of animals. The combination of 100 mg/kg of HBPG and 50 mg/kg of foscarnet protected 80% of mice from HSV2 encephalitis, whereas simple addition of the compound effects would be expected to protect 30% of animals.

Again, synergy is found with respect to a combination of HBPG and cidofovir (see Table 4), and acyclovir (see Table 6). These synergistic and unexpected results are exactly the type of evidence the U.S. Supreme Court has suggested are useful to rebut an obviousness rejection in KSR v. Teleflex, 550 U.S. ___, 127 S. Ct. 1727 (2007). Thus, applicant respectfully submits that these unpredictable results render the claimed inventions patentable, and respectfully request that the rejection be withdrawn.

CONCLUSION

Applicant submits that all claims are in condition for allowance, and respectfully request a Notice of Allowance.

All fees are being paid concurrently herewith, including the three-month Petition for Extension of Time Fee on the Electronic Filing System (EFS) by way of Deposit Account

authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket Number 07917-183001.

Respectfully submitted,

Date: 12/13/07

REG. NO. 54,112

J. Peter Fasse
Reg. No. 32,983

Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (617) 542-8906
21802078.doc